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Review

Natural killer cell memory in context

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ABSTRACT

Immune memory has traditionally been considered a hallmark of vertebrate T and B lymphocytes. However, given the advantage in mounting quicker and more robust responses to recurrent infection, it is unsurprising that alternative strategies of memory are found in various immune cells throughout the evolutionary tree. In this context, a variety of NK cell memory subsets have recently been identified. Mouse models of cytomegalovirus infection have been instrumental in revealing the kinetics and molecular mechanisms of long-lived NK cell memory. Moreover, murine liver-resident memory NK cell subsets have been identified that potentially harbour antigen-specificity. Phenotypic counter-parts have recently been characterised in the human liver, adding to the mounting evidence suggesting that a spectrum of NK cell memory subsets exist in primates. These include cytomegalovirus-associated peripheral blood NK cell expansions that in humans have been shown to harbour epigenetic alterations that impact cellular phenotype and function. Here we discuss some general mechanisms of non-classical immune memory. We highlight themes of commonality that may yield clues to the molecular mechanisms of NK cell memory, whilst emphasising some outstanding questions.

Contents

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; BM, bone marrow; CMV, cytomegalovirus; CRISPR, clustered regularly-interspaced short palindromic repeat; crRNA, CRISPR RNA; DTH, delayed-type hypersensitivity; HSCT, haematopoietic stem cell transplantation; ITAM, immunoreceptor tyrosine-based activation motif; NK, natural killer; PAM, protospacer adjacent motif; PI3K, phosphoinositide 3-kinase; PKCη, protein kinase C isoform eta; R protein, resistance protein; rasiRNA, repeat associated small interfering RNA; ROS, reactive oxygen species; RISC, RNA-induced silencing complex; SAR, systemic acquired resistance; SLEC, short lived effector cell; TLR, toll-like receptor; TF, transcription factor; VLR, variable lymphocyte receptors.

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1. Introduction

Immune memory is defined as more rapid and robust responses towards previously encountered antigens. Historically, immune memory was considered to be the preserve of T and B lymphocytes that possess unique antigen-specific receptors. During T and B lymphocyte development, a vast, clonally distributed, antigen receptor repertoire is generated by RAG-mediated somatic recombination of antigen receptor genes. This receptor diversity forms the basis for cellular selection, expansion and differentiation processes that underlie so-called classical, "adaptive" immune memory. The Rag1/Rag2 gene complex is almost exclusive to jawed vertebrates – a structural homologue also exists in purple sea urchin – originating from horizontal transfer of the Rag1 transposase into a common ancestor [1,2]. As such, adoption of Rag genes may have supported the evolutionary success and radiation of vertebrates. In contrast, natural killer (NK) cells were initially described in mice as a lymphocyte subset reactive to tumour cells without prior sensitisation [3,4]. Their inherent ability to reject tumour cells or bone marrow cells from MHC class I mismatched hosts distinguished them from adaptive T and B cells, that required antigen priming. Instead, NK cell activity is controlled by a repertoire of germ-line encoded receptors [5]. NK cells are therefore considered an innate arm of the immune system. However, it has been argued that the terms "adaptive" and "innate" immunity create artificial conceptual barriers [6]. Furthermore, a variety of acquired reactions to allografts or pathogens have been documented in species that lack RAG [7]. Thus, different mechanisms of adaptive immune memory must have arisen throughout evolution.

Recently, molecular mechanisms underlying immune memory have been elucidated in a variety of organisms. NK cell adaptations sit within this wider context of "non-classical" immune memory, which together with the well-studied mechanisms of T and B cell memory, reveal overlapping features that potentially offer molecular insight into NK cell memory formation. Here, we briefly review key molecular aspects forming cytotoxic $CD8^+$ T cell memory, an MHC class I-restricted lymphocyte subset representing "classical" immune memory that forms a functional complement to cytotoxic NK cells and therefore offers a platform for comparison within this review. Moreover, we discuss insights to the molecular mechanisms governing non-lymphoid immune memory in a range of different organism, providing a framework for understanding so-called "non-classical" immune memory. In greater detail, we review the growing body of work concerning NK cell memory. We aim to emphasise the phenotypic characteristics that define a spectrum of NK cell memory subsets and highlight some of the key questions that remain outstanding.

2. Formation of classical immune memory in cytotoxic $CD8^+$ T cells

Studying "classical" memory of T and B cells has provided enormous insight into the molecular mechanisms that generate immune memory. B cell memory for example, is marked by high affinity antibody responses through processes of isotype switching and somatic hypermutation. However, cytotoxic $CD8^+$ T cells most closely resemble NK cells in terms of gene expression profile and ability to kill target cells [8] and therefore invites comparison. In response to pathogens, cytotoxic $CD8^+$ T cells differentiate from naïve to either short-lived effector or long-lived memory cells via characteristic check-point phases of expansion, contraction and memory formation [9,10]. Naïve $CD8^+$ T cells are primed through a sustained interaction with dendritic cells presenting antigen in the context of co-receptor engagement and inflammatory cytokines including IFN-I, IFN-γ, IL-2 or IL-12 [11]. This tripartite signal induces cell proliferation; increasing the frequency of antigen-specific T cells by up to 50,000 fold [10]. During this time, T cell metabolism changes from oxidative phosphorylation to anabolic glycolysis, providing substrates necessary for proliferation and activation. The metabolic switch is regulated through hubs mTORC1/2, key regulators of protein synthesis, induced by upstream PI3K-AKT signalling [12,13].

The majority of expanding $CD8^+$ T cells differentiate into short-lived effector cells (SLECs), which combat the invading pathogen, but quickly recede via apoptosis [14]. The pro-apoptotic BH3 family member Bim appears to be a critical factor in this process [15]. The contraction phase typically removes 95% of expanded cells, leaving a small pool of memory precursor T cells that exhibit a less differentiated $CD62L^{hi}IL\text{-}7R^{\alpha hi}KLRG1^{lo}$ phenotype [9]. Notably, naïve $CD8^+$ T cells do not seem to have a pre-determined fate for either SLEC or memory cell lineages, as single cell experiments reveal the multi-potent potential of individual naïve cells [16].

The initial cues that determine SLEC versus memory precursor cell fate remain controversial, but likely depend on variations in signalling frequency, strength and duration, factors governed by antigen affinity and availability [9,17]. Alternatively, the asymmetric distribution of signalling proteins in dividing daughter cells may also influence $CD8^+$ T cell fate [18]. In this scenario, a synapse with an antigen-presenting cell polarizes the T cell, whereby surface receptors, intracellular signal molecules and possibly transcription factors maybe unequally distributed during cell division.

Several transcription factors drive a memory cell programme, forming a self-reinforcing network that maintains lineage identity [19]. The transcription factors Eomes and T-bet are both important in the early stages of $CD8^+$ T cell differentiation, however the ratio of Eomes to T-bet is critical in deciding a memory versus a SLEC programme [20,21]. Memory precursors dominantly express Eomes, whilst suppressing T-bet. The Wnt pathway and downstream TCF-1 transcription factor is necessary for Eomes expression [22,23]. Whilst the repression of T-bet is in-part mediated by FOXO1 activation [24]. FOXO1 is itself repressed by the PI3K-AKT-mTOR signalling axis that controls metabolic remodelling in expanding/SLEC T cells [24,25]. The induction of PI3K-AKT-mTOR signalling is dependent upon TCR engagement and further sustained by IL-12 through PI3K and STAT4 signalling [21,26]. In contrast, memory $CD8^+$ T cells express FOXO1 as they return to an oxidative phosphorylation energy supply [9], hence FOXO1 is an important sensor that links metabolism to gene regulation and cell fate. FOXO1 also induces KLF2, a transactivator that promotes expression of CCR7, CD62L [27], proteins required for homing.

$CD8^+$ T cell memory precursors express the signature transcription factors ID3 and BCL6. ID3 maintains cell survival [28], while BCL6 antagonises the SLEC specific regulator BLIMP-1 [19]. Whilst STAT4 appears to promote SLEC differentiation, STAT3 signalling via IL-10 and IL-21 play a critical role in driving $CD8^+$ T cell memory by maintaining expression of other transcription factors including Eomes and BCL6 [29].

Memory $CD8^+$ T cells can be classified into central, effector and tissue-resident memory compartments [30,31]. Central memory T cells recirculate through secondary lymph nodes, display a $CD62L^{hi}CCR7^{hi}$ phenotype, have low cytotoxic function, but high proliferative potential [32]. Conversely, effector memory T cells reside in the periphery, are $CD62L^{low}CCR7^{low}$ and constitutively express effector molecules such as granzyme B, but have lower proliferative capacity [32]. Finally, tissue-resident memory T cell subsets closely resemble effector memory T cells but are less migratory. Instead they are retained within tissues such as the lung, skin and gut via receptors CD103 and CD69 as well as other adhesion and chemokine receptors [9,30].

Memory T cells can confer life-long protection, with evidence of vaccination-induced responses lasting for over 85 years [33]. Mem-

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ory T cells are durably maintained via homeostatic proliferation enabling self-renewal and survival [34]. Homeostasis is dependent upon cytokines IL-7 and IL-15 but is antigen-independent [35,36]. Expression of the IL-2 receptor β-chain, a component of the IL-15 receptor is regulated by Eomes and T-bet, whilst the IL-7 receptor is regulated by KLF2 [27].

3. Non-classical immune memory

Early genetic analysis nurtured a dogma of adaptive immunity, distinguished by genes encoding RAG, MHC, TCR and BCR, being unique to higher order vertebrates. However, given the *prima facie* value in remembering previous pathogen encounter, it is perhaps unsurprising that alternative strategies of immune memory are found throughout the evolutionary tree. Recent studies have highlighted the existence of adaptive immune memory in a variety of species including bacteria, plants and jawless fish as well as T/B cell independent memory in mammals. The following examples are discussed as a framework to NK cell memory.

3.1. Bacterial immune memory

Most archaea and many bacteria achieve adaptive immunity via the CRISPR mechanism. Here, segments of invading phage DNA are incorporated into 'spacer arrays' that guide nucleases Cas1/2 to the targeted destruction of viral DNA upon re-exposure [37].

Bacterial CRISPR/Cas memory is analogous to the mechanism of RNA interference in eukaryotes, which also features nucleotide specific silencing via the endonuclease activity of the RNA-induced silencing complex. Moreover, it is becoming increasingly clear that miRNAs play critical roles in the generation of memory. In T cells for example, miRNA–17 ~ 92 is linked to SLEC and memory CD8 T cell fate by regulating the proliferation rate during expansion, with miRNA–17 ~ 92 expression correlating to signalling via PI3K-AKT-mTOR [38]. As will be discussed, a role for miRNA-155 has also been identified in NK cell memory, representing a first miRNA required for immune memory (section 5). Likewise, rasi RNAs, which include Piwi-piRNA species may also potentiate memory generation through more general mechanisms of epigenetic regulation and maintenance of heterochromatin [39].

3.2. Plant immune memory

Plants also possess siRNA and miRNAs that confer memory specifically to viral and bacterial invaders [40]. In addition to RNA interference mechanisms, plants exhibit a phenomenon known as systemic acquired resistance (SAR) that provides protection to pathogens mediated by intracellular sensors termed resistance (R) proteins [41]. R proteins bind either pathogen derivatives directly or instead monitor ('guard') a set of self-proteins that are common targets of pathogen-induced modification. In this way, a small repertoire of R proteins can detect 'modified-self' and react to a broad range of pathogens. Upon ligand binding, R proteins initiate kinase cascades that direct the release of extracellular signals such as salicylic acid. Distal plant cells detect these systemic signals, which in turn governs the secretion of antimicrobials or induce apoptosis of infected cells [42].

Strikingly, pathogen detection induces a cross-protective immune state termed SAR that can persist over several months [41,43]. Although the full mechanism of SAR memory has not yet been fully mapped, it is thought that distal plant tissue are primed following initial pathogen exposure through the acquisition of additional MAP kinase signalling proteins and extensive reprogramming of cells towards immune defence at the expense of photosynthesis and growth [44,45]. A master regulator of reprogramming is the salicylic acid binding transcriptional cofactor NPR1 (nonexpresser of pathogenesis-related protein 1). In addition, NPR1 directs epigenetic modifications at the promoters of immune defence genes [46,47]. Epigenetic marks thereby prime genes for amplified responses to secondary encounter [44]. Specifically, histone acetylation and H3K4 trimethylation marks, usually associated with gene activation, are deposited at the promoters of pathogen responsive WRKY transcription factors, but without inducing gene expression [47]. Instead, the WRKY genes are 'poised', ready for rapid response to repeat infection. The WRKY transcription factors are a family of 74 proteins with diverse roles including development, germination and stress response. Five of the WRKY transcription factors potentiate the SAR response amongst which NPR1 itself is targeted [48]. Gene expression analysis in plants treated with a salicylic acid homologue revealed over 2000 genes regulated by NPR1, of which 20% were also dependent upon WRKY18 [47]. Hence histone regulation of WRKY factors illustrates the role of epigenetics in harbouring durable immune memory.

Moreover, it is thought that pathogen stress induces an epigenetic led instability within R protein clusters that drive receptor diversification and duplication [49]. Finally, the importance of epigenetic mechanisms are further highlighted by the ability of viral RNAs and plant siRNAs to specifically silence gene expression through DNA methylation and histone repression, which likely provides defence against transposons [40].

3.3. Jawless vertebrate memory

Jawless vertebrates such as hagfish and lamprey evolved approximately 500 million years ago, some 100 millions years before the appearance of jawed-vertebrates [50]. Studies conducted in the late 1960s revealed that hagfish were capable of a delayed-type hypersensitivity reaction and rapidly reject skin allografts following priming [51,52]. These traits suggested that hagfish/lamprey have adaptive immunity with memory potential. However, later transcriptional analysis failed to identify components synonymous with classical, adaptive immunity such as TCR, BCR, RAG or MHC-I/II genes. Nonetheless, these jawless vertebrates possessed an alternative mechanism of adaptive immunity based on expression of highly diverse 'variable lymphocyte receptors' (VLRs).

Three VLR genes namely VLR-A, VLR-B and VLR-C have been identified each containing a large non-coding region bordered by a cassette consisting of hundreds of LRR modules [53]. The LRR modules are randomly incorporated into the VLR gene replacing the non-coding region to generate a receptor repertoire equivalent in diversity to mammalian antibody [50]. Moreover, the VLR-A receptor is exclusively expressed by T lymphocyte-like cells that possess transcription factors GATA-2, GATA-3, BCL11 B and TCF-1. These transcription factors are not only critical to mammalian T cell lineage commitment; they also influence formation of classical immune memory. In $CD8^+$ T cells, the transcription factor BCL11 B is required for initial antigen-driven expansion [54], GATA-3 is required for IL-7 receptor expression necessary for homeostatic maintenance, whilst TCF-1 for Eomes expression [22,55].

Likewise, VLR-B^+ cells represent a B-cell like lymphocyte, co-expressing Toll-like receptors (TLRs) and defined by transcription factors PAX5, BCL6 and BLIMP1. Further, upon appropriate antigen stimulation, plasma cells secrete soluble VLR-B antibodies. In mammals, BLIMP1 antagonises BCL6, which is instrumental in deciding effector versus memory fate in $CD8^+$ T cells as well as B cells [56]. Hence, jawless fish already possess many of the transcriptional components that are necessary to higher order vertebrate immune cell memory.

Finally, VLR-C^+ cells are mostly confined to skin and intestinal epithelium and are reminiscent of γδT cells in humans.

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The division of T cell-like and B cell-like lymphocytes each with signature transcription factors is suggestive of sophisticated gene regulatory networks maintaining these subsets akin to mammalian lymphocytes. Crucially, this indicates the existence of conserved lymphocyte-like cell types that predate the jawless fish lineage. As such, lymphocyte specialization does not appear to impinge on RAG-dependent antigen receptor recombination. Further studies will be required to characterise memory cells, which may include NK-like cell subsets. Ultimately, jawless fish models may yield vital clues as to the aetiology and maintenance of lymphoid memory.

3.4. Monocyte 'trained' memory

Studies in the Netea laboratory have revealed memory potential within subsets of monocytes, that like plants and jawless fish feature extensive transcriptional programming and associated epigenetic modifications. Here, memory cells termed 'trained monocytes' mediate cross-protective responses when primed by the Bacillus Calmette-Guérin (BCG) vaccine in humans or *Candida albicans* vaccine in mice [57]. Monocyte training relies on NOD2 and Dectin-1 receptor engagement with *C. albicans* derived cell wall component β-glucan [57,58]. Ligand binding initiated critical Raf-1 signals, whilst canonical Dectin-1 signalling mediated by Syk appeared to be dispensable for monocyte training. Like antigen receptors in T cells that contain ITAM clusters necessary for signalling, the dectin-1 receptor also possesses an ITAM-like motif that may activate Raf-1 [59]. Functionally, trained monocytes possessed increased production of pro-inflammatory cytokines such as TNF and IL-6 that correlated with stronger p38 MAPK signalling after TLR2 engagement.

Trained monocytes generated *in vitro* with β-glucan treatment revealed a widespread, orchestrated, transcriptional programme affecting some 7000 genes. Notably, this also included remodelling of metabolic pathways, a feature of classical T cell memory fate. Moreover, epigenetic analysis revealed histone H3K4 trimethylation deposition at promoters for TNF, IL-6, IL-18, TLR's and Dectin-1 receptors, a marker of promoter activity. The mechanisms meditating epigenetic remodelling are largely unknown, however the methyltransferase SETD7 was induced during monocyte training implying a role in establishing promoter trimethylation marks [57]. In addition, H3K27acetylation activity was induced in over 3000 distal regulatory elements such as enhancers, underlining the extent of the 'training' programme [60]. Thus primed monocytes are epigenetically hardwired to respond more robustly to pathogen stimuli. Indeed, epigenetic remodelling is likely an intrinsic mechanism to permit long-term maintenance of memory.

In addition to the examples of non-classical memory described, various NK cell subsets have also been found to exhibit features of memory and even antigen-specificity in humans and murine models. We will now discuss the features of NK cell memory and outline some key question remaining in the field.

4. Hepatic NK cell memory

Delayed-type hypersensitivity (DTH) reactions, traditionally attributed with antigen-specific T cell responses, can be modelled using haptenated antigens. Here, topical skin application of chemical modifiers such as oxazolone results in a novel hapten to which both priming and recall memory responses can be assessed. Unexpectedly, when Von Andrian's group applied such a mouse model in a RAG knockout background, a DTH memory response was preserved [61]. In contrast, mice failed to elicit a hypersensitivity response in a combined RAG and IL-2 receptor γ-chain deficient background, which lack the entire lymphocyte compartment. Furthermore, $SCID_{beige}$ mice, which have a mutation in *Lyst*, a gene required for cytotoxic granule biogenesis, were also unable to generate DTH responses [62]. Through genetic and cellular transfer experiments, NK cells were found to not only mediate hypersensitivity but be selective to the initial priming hapten, displaying specificity akin to T cells, despite ostensibly possessing a fixed repertoire of germ-line encoded receptors [5].

The NK cells mediating the DTH were curiously found exclusively in the liver, expressing the liver-homing chemokine receptor CXCR6, in combination with Thy1 (CD90) and Ly49C/I [61,63]. These hepatic NK cells could be adoptively transferred to naïve mice in relatively small numbers and yet mounted rapid recall responses within an hour of hapten rechallenge [62]. Blocking experiments revealed that both the CXCR6 receptor and its ligand CXCL16 were critical to mount a hapten memory response [63]. Knockout murine models showed that hapten specific memory was further dependent upon the inflammatory cytokines IL-12, IFN-α and IFN-γ [62]. Notably, this antigen-specific memory appears to be durable, lasting at least 3 months after priming [63].

Similar NK cell memory responses have also been observed towards virus-like particles ectopically expressing antigens to influenza A, vesicular stomatitis virus and HIV [63]. Further, when vaccinated with live vaccinia virus, hepatic memory NK cells conferred protection from a lethal dose challenge, that, like the hapten-primed NK cells, could also be adoptively transferred to naïve mice [64]. Analogous protective responses are observed in a mouse model of genital HSV-2 infection with memory NK cells possessing potent IFN-γ responses towards virally infected cells compared to naïve NK cells [65].

Transcriptional profiling of hepatic mouse NK cells identified two distinct phenotypes occupying the liver, distinguished by reciprocal expression of CD49a and DX5 [66]. However, only the minor $CD49a^{+}DX5^{-}$ NK cell population, expressing high levels of CXCR6, had the capacity for hapten specific memory. Surface analysis revealed that these cells also expressed CD69, an activatory receptor associated with lymph node retention [67], but low KLRG1 and CD62L receptor expression, markers correlating with replication and differentiation. In addition, the $CD49a^{+}DX5^{-}$ NK cells had low expression of transcription factor Eomes, normally associated with NK cell maturity [68], but high expression of transcription factors Egr2 and Ikzf2 (encoding Helios) [66]. Interestingly, the same study indicated that the memory NK cell subset originated from a hepatic hematopoietic progenitor/stem cell and was not bone marrow (BM) derived like splenic or peripheral NK cells. This lineage dichotomy has also been highlighted in an Eomes reporter mouse, revealing the mutual exclusivity between Eomes and T-bet in regulating BM and liver-derived NK cell development [68,69]. Characterisation of hepatic NK cells highlighted the dependency of transcription factor T-bet in restricting lineage maturation of both foetal and adult NK cells [68]. The dominance of T-bet over Eomes expression within NK cell memory subsets is in direct opposition to the establishment of $CD8^{+}$ T cell memory, where the reverse trend is observed [20,21].

Recent experiments have hinted at memory potential within hepatic NK cells of primates. Rhesus macaques vaccinated with either SIV or SHIV exhibited preferential NK cell killing of target cells possessing viral antigens matching the virus used for vaccination compared to mismatched virus [70]. Target cells consisted of autologous DCs loaded with either the SIV derived Gag antigen or SHIV derived Env antigen. Although differences between matched and mismatched antigen responses were relatively subtle, they were extremely long-lived, detected five years after initial vaccination. Further experiments will be necessary to demonstrate enhanced or protective responses *in vivo*.

Hepatic memory responses have so far not been directly observed in humans. However, phenotypic counterparts have been described expressing CXCR6, CD49a and CD69 with concomitant

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expression of T-bet and low Eomes expression, consistent with mouse DX5$^-$ hepatic cells [71,72]. In addition, these CD49a$^+$ hepatic NK cells express the NKG2C activating receptor, associated with CMV virus driven NK cell expansions [73,74]. The CD49a$^+$ hepatic NK cells demonstrate increased effector cytokine capacity but poor degranulating ability when stimulated [72]. Notably, the CD49a$^+$ hepatic NK cells represent a minority fraction compared to CD49a$^-$ liver NK cells and were detect in 13/29 healthy donors. Whether these cells have memory potential remains to be determined.

Together, several key questions remain with regard to the nature of hapten-specific liver NK cells, including the mechanism that generates antigen-specificity from a supposedly fixed repertoire of germ-line encoded genes and their relative contribution to immune memory responses. Another objective is to fully understand the dynamics of hepatic NK cell migration. The hapten-specific responses cause local inflammation at the site of epidermal application, normally the ear, which is at odds with a pool of liver resident NK cells. How these NK cells are able to scrutinize the periphery and respond so rapidly still needs to be defined. There is evidence that dendritic cells may shuttle haptenated antigens to lymph nodes [75], wherein dendritic cells and NK cells are already known to occupy the same medulla and paracortex lymph node regions mediating NK cell activation via IL-12 and IFN, cytokines also critical in hapten DTH [76]. However, the dependency of dendritic cells to NK cell hapten responses is still unconfirmed, and tracking the rapid kinetics of inflammation, which can be as little as 30–60 min after hapten exposure will be crucial. Interestingly, both human and mouse hepatic NK cells show poor degranulating potential [66,72], consistent with the relatively low responses seen in rhesus macaques [70]. Thus, it is unclear if direct target cell cytotoxicity is important to hepatic memory. Nevertheless, the fact that $SCID_{beige}$ mice are incapable of mediating the DTH reaction warrants further investigation of the inflammatory mechanism of DTH [62].

5. NK cell memory to mouse CMV

In a B6 mouse model of MCMV infection the NK cell response to virus is monopolised by cells expressing Ly49H, an activating receptor dedicated to binding the virally encoded glycoprotein m157 [77,78]. Hence, this interaction represents a rare example of NK cell antigen-specificity, contrasting to hepatic NK responses described above, where no discernable antigen receptors have been identified. The laboratories of Lanier and Sun have eloquently exploited MCMV responses to map the dynamics of NK cell antigen-specific memory formation. Initially, Ly49H$^+$ NK cells were adoptively transferred to recipient mice lacking the DAP12 adapter, necessary for Ly49H expression. Upon subsequent MCMV infection, the minority Ly49H$^+$ population rapidly proliferated 2–3 log fold in the spleen and liver, peaking at around day 7, before entering a contraction phase which ultimately spawned a smaller but persistent population of memory cells, observed 70 days post infection [79]. This memory population was approximately 10 times more potent in conferring protection against re-infection compared to naïve cells and had a self-renewing capacity, as measured by BrdU uptake [79]. The rapid expansion followed by a gradual contraction mirrored the kinetics of memory CD4$^+$ T cells, as opposed to the abrupt decline observed in memory CD8$^+$ T cell formation [14,80].

A series of targeted knockout mouse models have been used to further delineate the phases of NK cell memory. Mechanistically, the initial expansion phase is dependent on the NK cell co-activating receptor DNAM-1, presumably as a prerequisite to the recognition of MCMV infected cells. Indeed, lymph node macrophages and dendritic cells both rapidly induce DNAM-1 ligands upon MCMV infection [81]. Crucially, DNAM-1 knockout mice or antibody blocking abrogated MCMV driven memory. Examination of signalling downstream of DNAM-1 receptor engagement revealed that the serine-threonine protein kinase C isoform eta (PKCη) and Src-family tyrosine kinase Fyn had distinct contributions to memory formation [81]. Whilst both signalling adapters were necessary for optimal NK cell memory generation, PKCη but not Fyn, was indispensable to proliferative expansion. It has since been confirmed that Fyn plays a redundant role with other Src kinases, including Src, Lyn and Lck in phosphorylating the key downstream DNAM-1 target Grb2 [82].

Knockout mouse models have further revealed the absolute requirement for inflammatory cytokine IL-12 and its signalling counterpart STAT4 to NK cell expansion and memory generation [83]. Recent evidence suggests IFN-I also plays a role in virus-induced expansion and protection from fratridcide, but is dispensable for memory generation itself [83,84]. Moreover, cytokines IL-12 and IL-18 were also shown to transactivate miRNA-155 expression, which in turn, represses SOCS1, a regulator of T cell homeostasis, and Noxa, a pro-apoptotic Bcl2 homology domain (BH3) protein [85]. In T cells, miRNA-155 is required for effector CD8$^+$ T cell function to viral and cancerous cells by maintaining STAT5 signalling through inhibition of the SOCS1 repressor [86]. The role of STAT5 signalling in NK cell memory formation has not yet been resolved.

The driver of the proliferative burst itself is coordinated by the transcription factor ZBTB32, a BTB-zinc finger in the same family as PLZF (a key differentiation factor of MAIT, NKT and γδ T cells), ThPOK and MAZR (both CD4$^+$ and CD8$^+$ T cell fate determinants) [87,88]. Notably, ZBTB32 is induced upon IL-12 and IL-18 stimulation and subsequently antagonises the BLIMP1 transcription factor, known to be a critical suppressor of NK cell division and memory formation. Indeed, BLIMP-1 appears to play a ubiquitous role within lymphoid cells in driving effector cell lineages at the expense of memory formation [56].

Following proliferation, most of the responding NK cells are removed via the activity of the pro-apoptotic protein Bim [89], a factor associated with T cell contraction [15]. Bim knockout mice are unable to reduce the effector pool and retain an immature KLRG-1$^-$ cell phenotype [89]. The selection of persistent memory cells from a contracting pool of effectors seems to be influenced by a process of mitophagy. Here, damaged mitochondria accumulated during the stress of cell division, increase the intracellular concentration of reactive oxygen species (ROS) [90]. To prevent ROS mediated cytotoxicity, mitochondria are shuttled into autophagasomes governed by BCL2 family members BNIP3 and BNIP3 L activity. Both BNIP3/3 L knockouts prevent MCMV NK cell memory, whilst pharmacological induction of mitophagy boasts NK cell survival [90].

NK cell antigen-specific recognition of MCMV has been an instrumental tool in evaluating mechanisms and dynamics of memory formation. However, in the absence of other antigen-specific receptor models it remains to be determined whether these discoveries represent general principles of NK memory or instead are context specific to MCMV. For example, is there an absolute requirement for a DAP12 coupled receptor together with DNAM-1 signalling to spawn memory or can a synergy between other receptor pairs compensate?

MCMV induces rapid NK expansion with 100-fold division in spleen and 1000-fold in liver, underlining that memory can be generated within multiple tissues. Whether there are stable differences in the quality or homing ability within the NK cell memory compartment akin to T cell central and effector memory subsets remains to be determined. The finding that mitophagy influences memory formation is interesting, however there are likely other factors that instruct NK memory cell fate. In this regard, differences in signalling thresholds or signalling duration may dictate memory survival as evidenced in classical T cell differentiation,

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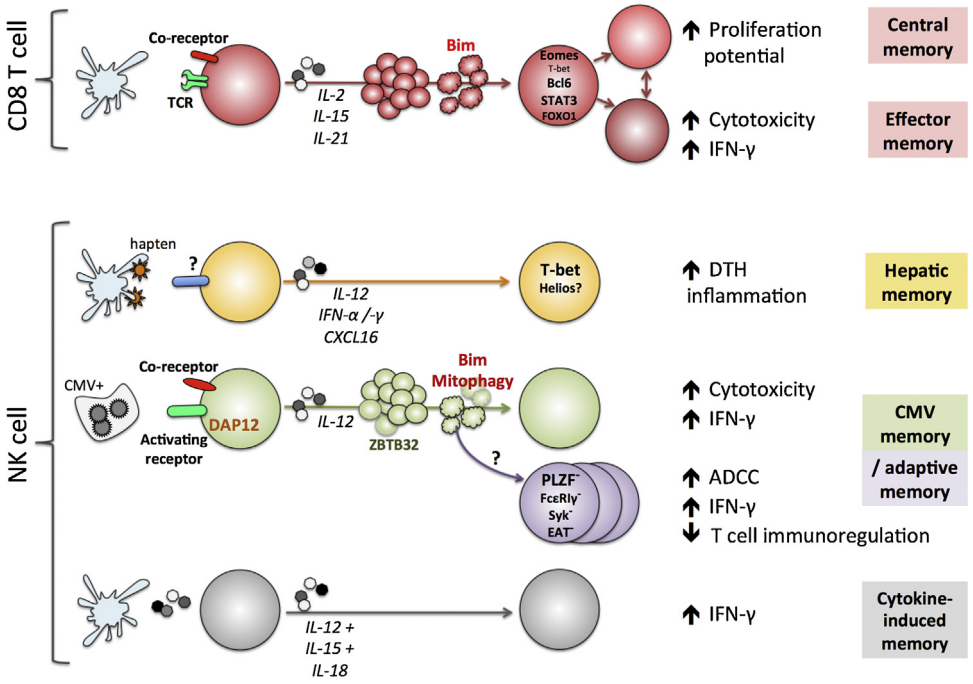

Fig. 1. Comparison of mechanisms generating CD8⁺ T cell versus NK cell memory subsets. Naïve CD8⁺ T cells (red) undergo rapid expansion following APC presentation of peptides together with co-activating stimulation in the context of proinflammatory cytokines. A contraction phase follows whereby the majority of differentiated cells are eliminated via Bim-dependent apoptosis. Finally, interconvertible central memory and effector memory subsets, that have a less differentiated phenotype, persist long-term via homeostatic proliferation. By comparison, a variety of NK cell memory subsets have now been identified. Antigen-specific hepatic NK cell memory (yellow) is driven in response to haptenated proteins or viral antigens via an undefined molecular process. CMV-induced NK cell memory (green/blue) resembles CD8⁺ T cell differentiation. In mice, differentiation is induced upon engagement of the DAP12-associated Ly49H receptor together with DNAM-1 receptor co-stimulation in the context of STAT4-mediated IL-12 cytokine signalling. Cell proliferation is promoted by ZBTB32 transcription factor, followed by a contraction phase dependent on Bim-mediated apoptosis instructed by mitophagy. In humans, adaptive CMV-associated NK cell memory subsets (blue) have an undefined aetiology. They are distinguished by loss of PLZF transcription factor, which accompanies loss of intracellular signalling adapters that are epigenetically silenced. The adaptive subset display increased antibody-dependent cellular cytotoxicity (ADCC), whilst loss of signalling adapters reduces their capacity for autologous recognition of expanded T cells that are mounted during infection. Cell intrinsic cytokine-induced memory can be established through a combination of cytokines IL-12, IL-15 and IL-18, promoting increased IFN-γ production upon restimulation. Functional attributes and transcription factors associated with specific memory subsets are annotated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

whilst metabolic changes that potentially affect transcriptional programmes could also be investigated.

6. Human NK cell memory-like responses to CMV

Contrasting initial studies suggesting a short life-span of NK cells [91], a number of recent studies that have been able to follow NK cell dynamics and phenotype post viral infection and are suggestive of long-term expansions of unique subsets of memory-like NK cells not found in naïve hosts. Critically, these subsets appear to be either driven by HCMV directly or are secondary to HCMV reactivation. Alternatively other viruses may activate NK cell pools that have previously been shaped and/or maintained by HCMV.

HCMV persists as a life-long latent infection in the majority of the population, hence is difficult to track initial exposure or virus specific responses. However, CMV re-activation following haematopoietic stem cell transplantation (HSCT) provided a unique opportunity to characterise NK cell responses during active HCMV infection [74,92]. In these studies an NKG2C^{hi} subset expanded during active disease and had an NKG2A^{-}CD57^{+}KIR^{+} phenotype that was stably identified over a year after transplant. The activating NKG2C receptor and the inhibitory NKG2A receptor both bind to HLA-E, the surface expression of which can be enhanced by HCMV UL40 glycoprotein [94]. Further, this memory-like subset had increased capacity for IFN-γ, which correlated to elevated T-bet expression. The DAP12-coupled NKG2C receptor is strongly associated with HCMV infection, but not other herpes virus family members EBV or herpes simplex [73,93]. Further the expansion of NKG2C^{hi} cells is promoted in NK cell subsets that express educating KIR, inhibitory self-receptors that potentiate NK cell function. Likewise activating KIR receptors that signal via DAP12 were also associated with CMV driven NK cell subset expansion [94]. It is also noteworthy that DAP12 is an ITAM containing adapter, a feature of T cell antigen receptor as well as monocyte Dectin-1 signalling.

Interstingly, NK cells were longitudinally assessed during an outbreak of hantavirus, an acute viral infection with severe symptoms [95]. In CMV seropositive individuals, NK cells rapidly expanded mirroring kinetics of CD8⁺ T cells. Phenotyping of the expanding subset showed that it too was dominated by NKG2C^{hi} NK cells. Moreover the expanded subsets were readily identifiable over 60 months after initial infection [95]. Likewise, NKG2C^{hi} expanded NK cell subsets have been identified in other virus infections including HCV and HIV in which patients are also seropositive for HCMV [96–98]. It remains unclear if HCMV reactivation occurs alongside acute disease to drive subset expansion or alternatively HCMV shaped NK subsets expand in response to secondary viral infection alone, and may even be pathological (Fig. 1).

7. Adaptive NK cell memory

Strikingly, the NKG2C^{hi} population observed in HCMV seropositive individuals overlaps with a newly identified 'adaptive' NK cell subset that is characterised by the down-regulation of one or more intracellular signalling components, namely FcεRγ, SYK, and EAT-2, presumably as a result of viral (HCMV) interaction [99–101]. The allelic silencing of signalling proteins appears stochastic, depend-

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ing upon respective promoter DNA hypermethylation [100,101]. Indeed, widespread changes in the DNA methylation profile are evident within the adaptive pool, whereby CMV-associated adaptive NK cells epigenetically approximate differentiated effector $CD8^+$ T cells [101]. This parallels the examples of plant, monocyte and classical memory which also require significant reprogramming to establish immune memory [60,101].

The adaptive subset is further distinguished by lack of expression of the transcription factor PLZF (ZBTB16), normally present in all human $CD56^{dim}$ NK cells [101]. The surface phenotype of adaptive cells, as defined by loss of intracellular signalling molecules or PLZF deficiency, exhibits great inter-donor and intra-donor variability. Whilst $NKG2C^{hi}CD57^+CD161^-CD85j^+CD2^+NKp30^{lo}$ NK cells are prevalent, a phenotype previously attributed to HCMV imprinting [73], closer scrutiny reveals large phenotypic heterogeneity. For example, adaptive NK cells lacking NKG2C or CD57 expression are also readily detectable [101]. In contrast to acutely expanded NK cells, adaptive NK cells do not generally express activation markers such as CD69, CD38 or CD25 and represent a stable compartment over many months [99,101].

The presence of adaptive NK cell subsets is common, identifiable in approximately 50% of healthy HCMV seropositive European individuals, and in extreme cases this pool can stably occupy up to 90% of the overall peripheral NK cell compartment [101]. In the presence of viral antibodies derived from infected plasma, adaptive NK cells lacking FcεRγ expression exhibited greatly enhanced effector responses towards HCMV infected targets, with augmented IFN-γ and TNF production as well as target degranulation [99]. Enhanced responses were also observed towards HSV-1 infected targets in presence of HSV-1 viral antibodies suggesting these NK cells were, ostensibly, cross-protective to other viruses [99]. In the absence of viral antibodies, adaptive NK cells are generally poorer responders than conventional NK cells, especially to autologous stimulated $CD4^+$ or $CD8^+$ T cell targets. Adaptive NK cells may therefore enhance the overall quality and duration of immune responses by allowing unchecked T cell activation [101].

A number of key questions remain with regard to memory formation in humans, which are difficult to assess in the lack of a controlled environment. The stable, enduring appearance of virally induced subsets suggests memory-like properties, however the nature of 'self-renewal' in this context is unresolved. Likewise, the aetiology of these cells is currently unknown, but could possibly be addressed in primate models.

8. Concluding remarks

NK cell memory sits within an expanding field of non-classical memory responses that blur the historic definitions of innate and adaptive immunity. Further, it is useful to draw comparisons with the now numerous examples of immune memory, which offer both molecular insight and clues as to the evolutionary origins of NK cell memory. In this regard, the most striking parallels can be observed between classical $CD8^+$ T cell memory and CMV-induced NK cell memory formation, both in terms of kinetics of expansion/contraction and in the tripartite signalling which requires activating and co-activating receptor engagement in the context of cytokine.

It is interesting then that studies priming NK cells with pro-inflammatory cytokines alone, in the absence of antigen, have also revealed the intrinsic capacity of NK cells to acquire memory-like characteristics [102,103]. Specifically, a combination of cytokines IL-12, IL-15 and IL-18 results in augmented IFN-γ effector responses when NK cells are re-stimulated weeks later. Moreover, cytokine-induced NK cell memory can be transferred to daughter cells, suggesting epigenetic mechanisms that maintain durable memory. Indeed, epigenetic hardwiring likely underpins the persistence of immune memory subsets, as has been observed in plants, monocytes and classical memory cells [42,60,104]. Global DNA methylation analysis of the adaptive NK memory compartment have already illustrated the extensive epigenetic programming that determines their phenotype and functional characteristics [101,105].

Much work is required to fully map the epigenetic specific features within the different NK cell memory subsets. Importantly, how a variety of contextual signals, emanating from receptors for target cell structures as well as cytokines, direct remodelling of the epigenetic landscape within memory subsets remains to be explored. Harnessing NK cell memory in designing vaccination strategies towards pathogens and cancer may ultimately complement classical memory targeted responses.

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